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**Higher cardio-respiratory fitness is associated with increased mental and physical quality of life in people with bipolar disorder: a controlled pilot study**

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**Abstract**

The aim of this study was to investigate whether cardiorespiratory fitness among outpatients with bipolar disorder is associated with health related quality of life (HRQL) and explore differences versus healthy controls. Outpatients with bipolar disorder and healthy controls matched for age, sex and body mass index completed the 36-item Short Form Health Survey, the Positive-and-Negative-Affect-

Schedule (PANAS), a maximal cardiorespiratory fitness test, and wore a Sensewear Armband to measure physical activity and sedentary behavior for eight days. Unpaired t-tests, Pearson correlations and backward regression analyses were performed. Outpatients with bipolar disorder (n=20; 14♀; 47.9±7.9 years) had a significantly lower physical and mental HRQL than healthy controls (n=20; 14♀; 47.8±7.6 years), a lower maximum oxygen uptake (VO<sub>2</sub>max) and were more sedentary. While no significant correlates were found for HRQL in controls, higher VO<sub>2</sub>max values and lower PANAS negative affect scores predicted better physical and mental HRQL in people with bipolar disorder. The final regression model explained 68% and 58% of the variability in physical and mental HRQL respectively. Cardiorespiratory fitness is associated with mental and physical HRQL among people with bipolar disorder. The current study offers novel targets for scientific investigation and clinical interventions to increase HRQL in people with bipolar disorder.

**Keywords:** bipolar disorder; quality of life; fitness; physical activity

## 1. Introduction

Bipolar disorder (BD) is a chronic and severe mental illness with a life-time prevalence of approximately 2% (Stubbs et al., 2016). According to the World Health Organization global burden of disease study, BD ranks within the top 20 causes of disability among all medical conditions worldwide and 6<sup>th</sup> among all mental disorders (Whiteford et al., 2010). Of particular concern is the 10-year lower life expectancy as compared to the general population (Kessing et al., 2015a). Although the underlying causes for the increased risk for premature mortality are multi-factorial, it is well established that a higher risk for cardio-metabolic diseases plays a major role (Kessing et al., 2015b). Cardio-metabolic co-morbidity is increased in people with BD (Vancampfort et al., 2015 & 2016a) with psychotropic medication use (Correll et al., 2015) and unhealthy lifestyle behaviours (Bly et al., 2014; Martin et al., 2016; Vancampfort et al., 2016b & c) key contributing factors.

Unsurprisingly, the chronic nature, the recurrence of manic and/or depressive symptoms and the high prevalence of somatic co-morbidities have a major impact on the physical and psychological domains of health related quality of life (HRQL) of a person with BD (Bernstein et al., 2016; Jansen et al., 2013; Martín-Subero et al., 2014). HRQL is an important patient-rated outcome and is a measure

of the impact an illness has upon the functional health status as perceived by the patients themselves (IsHak et al., 2012). It is therefore an important target of interventions aiming to achieve functional recovery and identifying determinants of HRQL in people with BD is essential and may help improve the focus of multidisciplinary treatment. Previous research indicated that the presence of depressive symptoms (Michalak et al., 2013; Piccinni et al., 2007), somatic (Fenn et al., 2005; Kilbourne et al., 2009; Kolotkin et al., 2008) and psychiatric (e.g., the presence of anxiety) (Albert et al., 2008) co-morbidity, cognitive problems (Anaya et al., 2016), illicit drug use (Kilbourne et al., 2009), nicotine dependence and a lack of social support (Gutiérrez-Rojas et al., 2008) all have a profound negative impact on HRQL in people with BD.

There is a growing interest in the association between cardiorespiratory fitness and health and well-being among people with BD (Vancampfort et al., 2016d), yet to date, the impact of cardiorespiratory fitness on the HRQL of people with BD has not been investigated. This is surprising given the fact that people with BD have significantly reduced cardiorespiratory fitness levels ((Vancampfort et al., 2015b & 2016e), and that lower fitness levels are associated with difficulties in undertaking activities of daily life (Vancampfort et al., 2016f). Although the relationship between cardiorespiratory fitness and general health perceptions has been found in population-based studies (Sloan et al., 2009), research investigating this relationship among people with BD is lacking.

The aim of the current study was to examine the relationship between cardiorespiratory fitness and HRQL among people with BD and determine if this relationship differed compared to healthy controls. To this end, we first assessed the mental and physical HRQL, cardiorespiratory fitness and physical activity participation of people with BD compared with an age, gender and body mass index matched healthy population.

## 2. Methods

### 2.1. Participants and procedure

Over a 10-month period, consecutive adult (18-65 years) outpatients with a DSM 5 diagnosis of BD I or II (American Psychiatric Association, 2013) of the UPC KU Leuven, campus Kortenberg, in Belgium were invited to participate. Acutely psychotic patients and those with a DSM 5 diagnosis of substance use disorder during the previous 6 months were excluded. Somatic exclusion criteria included evidence of severe cardiovascular, neuromuscular and endocrine disorders, which, according to the American College of Sports Medicine (2013), prevented participants of being physically active as per usual. Healthy control subjects were recruited among acquaintances of the wider research team. These researchers were however unaware of the specific aims of this research (i.e. comparison of data with BD patients) and blinded from the test results of the patient population. All healthy controls were volunteers who received a general physical examination and were free of significant cardiovascular, neuromuscular and endocrine disorders that might hinder safe participation. An independent statistician performed the matching for age, gender and body mass index (BMI). The study procedure was approved by the Scientific and Ethical Committee of the UPC KU Leuven, campus Kortenberg, Belgium and conducted in accordance with the principles of the Declaration of Helsinki. All participants gave their informed written consent. There was no compensation for participation in the study.

### 2.2. Anthropometric assessments

Anthropometric measurements included body weight and height. Body weight was measured in light clothing to the nearest 0.1 kg using a SECA beam balance scale, and height to the nearest 0.1 cm using a wall-mounted stadiometer.

### 2.3. Medication use

Data on current use of antidepressants, mood stabilizers and antipsychotics was collected from the medical records. Daily dosage of each antipsychotic was converted into a daily equivalent dosage of chlorpromazine following the consensus of Gardner et al. (2010). If patients were treated with a

combination of antipsychotics, all obtained equivalent dosages of chlorpromazine were summed together. We did not include the daily dosage of mood stabilizers in the statistical analyses if the same mood stabilizer was not present in at least 10 participants.

#### *2.4. Cardiorespiratory fitness testing*

Graded exercise tests were conducted to measure cardiorespiratory fitness. All tests were performed on a cycle ergometer (Siemens-Elema 380B; Ergometrics 800S, Ergometrics, Bitz, Germany) in an air-conditioned laboratory where the room temperature was regulated at 18-22°C. Tests were supervised by an experienced physiotherapist (PhD) blinded for the patient status and for other test results. Patients were asked to cycle at a constant rate of 60 rates per minute. The initial workload of 20W was increased by 20W every minute. Blood pressure was measured at rest, with the patient sitting on the bicycle, and every 2 minutes during the graded exercise test. Heart rate and a 12-lead electrocardiogram (Max Personal Exercise Testing®, Marquette, WI, USA) were registered continuously. In- and expired gasses were analyzed breath-by-breath by means of the Oxyxon Pro (Jaeger, Mijnhardt, The Netherlands). In order to define a maximal oxygen uptake ( $VO_2\text{max}$ ) (ml/kg/min) we followed the criteria described by the European Association for Cardiovascular Prevention and Rehabilitation (Mezzani et al., 2009). A maximal effort was assumed if the cardiopulmonary exercise testing was terminated by the patient due to exhaustion, dyspnea, pain or tiredness in the legs and if (1) a peak respiratory exchange ratio (RER)  $\geq 1.10$  and/or (2) a rating of perceived exertion  $\geq 16$  on the Borg Scale (Borg, 1998).

#### *2.5. Health related quality of life: the 36-item Short Form Health Survey (SF-36)*

The SF-36 health related quality of life questionnaire (Ware et al., 1993) assessed eight domains of functioning during the previous four weeks, including: physical functioning, role limitations due to physical problems, vitality, bodily pain, social functioning, role limitations due to emotional problems, in addition to mental and general health. Scores for the SF-36 range from 0 to 100, with higher scores indicating a better health related quality of life. The four domains: physical functioning, role limitations due to physical problems, bodily pain and general health were summarised into a physical component score, whereas the four domains energy/vitality, social functioning, role limitations due to emotional problems and mental health were summarised into a mental component score.

### 2.6. *The Positive-and-Negative-Affect-Schedule (PANAS)*

The PANAS (Watson et al., 1988) is a 20-item questionnaire assessing positive and negative affect and was chosen as a measure of usual daily mood. Ten items measure positive affect (e.g., excited, inspired) and 10 items measuring negative affect (e.g., upset, afraid). Each item is rated on a five-point Likert Scale, ranging from 1 = very slightly or not at all to 5 = extremely, to measure the extent to which the affect is experienced in general.

### 2.7. *Objective physical activity assessment: Sensewear Armband (SWA)*

The SWA was worn over the right arm triceps muscle and assessed minute to minute movement through multiple sensors, namely a two-axis accelerometer and sensors measuring heat flux, galvanic skin and near body-temperature. Data were combined with gender, age, body weight and height to estimate active energy expenditure using algorithms developed by the manufacturer (SenseWear Professional software, version 7.0). In accordance with the findings of Corder et al. (2008) who reported that behavioral modification often occurs on the first day of monitoring, data recorded on the initial day were discounted entirely and only the data obtained during the subsequent 7 full days were used. Several variables were calculated from the SWA data. Physical activity can be expressed in metabolic equivalents (MET; in kcal/hour/kg), an indicator of daily energy expenditure. The unit MET is used to estimate the amount of oxygen used by the body during physical activity. We calculated the mean daily active energy expenditure (AEE; in kcals:  $\geq 3\text{MET}$ ) as a measure for physical activity behavior and time spent in sedentary activities ( $\leq 3\text{MET}$ ). Data were accepted when the average on-body measuring time was at least 1368 minutes per day (95% of a 24-hour bout). The SWA provides valid and reliable estimates of energy expenditure (Fruin and Rankin, 2004).

### 2.8. *Statistical analyses*

Data were assessed for normality using the Shapiro-Wilk test and found to be normally distributed. Descriptive statistics are presented as mean and standard deviation (SD). Unpaired t-tests were used, to examine differences in characteristics between outpatients with BD and healthy controls. Next, Pearson correlation coefficients were calculated to estimate the strength of the associations between mental and physical HRQL and single variables of interest in outpatients with BD and healthy controls separately in order to explore any differences between both populations. All significant ( $P < 0.05$ )



correlates were included in backward multiple regression analyses in order to assess the total variance in physical and mental HRQL explained by all independent predictor variables. For the regression analyses a priori, the significance level was set at  $p < 0.1$ . Statistical analysis was performed using the statistical package SPSS version 22.0 (SPSS Inc., Chicago, IL).

### 3. Results

#### 3.1. Participants

A total of 28 consecutive outpatients with BD were invited to take part in the study. Three patients with co-morbid substance abuse during the previous six months were excluded. Two more were excluded as a consequence of a cardiovascular or neuromuscular disorder that might prevent safe participation. Of the 23 eligible outpatients with BD, three declined to participate (i.e., were not interested). None of the included patients dropped-out or were unable to complete the tests and twenty outpatients with BD were included in the final analysis. Twenty healthy controls, matched for age, BMI and gender completed the maximal cardiorespiratory fitness test, the SF-36 and the PANAS and worn the SWA. Participants' characteristics are shown in Table 1. In both groups there were 6 men and 14 women. Two outpatients with BD smoked (10 and 20 cigarettes per day) compared to one healthy control subject (10 cigarettes per day). Ten outpatients with BD were on antipsychotic medication (mean dose in chlorpromazine equivalents =  $367 \pm 217$  mg/day) while nine were treated with lithium carbonate (mean dose =  $755 \pm 292$  mg/day) and eight with lamotrigine (mean dose =  $225 \pm 128$  mg/day). Five outpatients with BD took antidepressants: escitalopram ( $n=2$ ), venlafaxine ( $n=1$ ), sertraline ( $n=1$ ), trazodone ( $n=1$ ). Somatic medication was taken by nine but none were on beta-blockers.

#### 3.2. Differences in clinical characteristics between outpatients with BD and matched healthy controls

Outpatients with BD had a significantly lower physical ( $P < 0.001$ ) and lower mental ( $p < 0.001$ ) HRQL. They also had a significantly ( $P = 0.047$ ) lower  $VO_2$ max ( $26.0 \pm 7.3$  ml/min/kg versus  $30.4 \pm 6.5$  ml/min/kg,  $P = 0.047$ ). While they were not significantly less physically active (expressed as mean daily active energy expenditure in a one-week period) ( $P = 0.42$ ) than healthy controls, they were more sedentary (expressed as mean time spent sedentary daily in a one-week period) ( $P = 0.001$ ). The average wear-

time of the SWA was 96.7% (range: 95.1%-99.9%) for the outpatients and 99.1% (96.7%-99.9%) for the healthy controls. Finally, outpatients with BD had significantly lower PANAS positive ( $P=0.015$ ) but not PANAS negative affect ( $P=0.072$ ) scores. Details are presented in Table 1.

### *3.3. Associations of clinical characteristics with physical and mental HRQL in outpatients with BD versus healthy controls*

While no significant correlates were found for the physical HRQL in healthy controls, among the patients with BD a higher physical HRQL score was significantly associated (all  $P<0.05$ ) with a higher  $VO_2$ max value, a lower BMI, higher active energy expenditure and lower sedentary behavior levels as assessed with the SWA. We also found that a higher physical HRQL score was significantly associated with higher positive and lower negative PANAS scores and lower antipsychotic medication doses (expressed in Chlorpromazine equivalents). Similarly, no significant correlates were found for the mental HRQL in healthy controls, but a higher mental HRQL score was significantly ( $P<0.05$ ) associated with a higher  $VO_2$ max value, higher active energy expenditure and lower sedentary levels as assessed with the SWA. Next to this, a higher mental HRQL was significantly associated with higher positive and lower negative PANAS scores in people with BD. Detailed  $r$ - and  $P$ -values are presented in Table 2.

### *3.4. Regressions analyses with physical and mental HRQL as independent variables in outpatients with BD*

Following the univariate correlation analyses, variables that significantly correlated with the HRQL domains were included in backward regression analyses. In outpatients with BD, higher  $VO_2$ max values and lower PANAS negative affect scores independently predicted better physical (see Table 3) and mental (see Table 4) HRQL outcomes. The final model explained 68% of the variability in physical HRQL and 58% of the variability in mental HRQL.

## 4. Discussion

### 4.1. General findings

To the best of our knowledge, this is the first study to investigate the association of cardiorespiratory fitness with the physical and mental domains of HRQL in a sample of outpatients with BD and healthy controls. The multidisciplinary treatment of people with BD has traditionally focused on psychiatric symptomatology. In this study, we found preliminary evidence that, next to a negative affect, also lower cardiorespiratory fitness levels in outpatients with BD are associated with lower physical and mental HRQL, whereas this relationship is not observed in healthy controls. It might, however, be hypothesized that the higher HRQL scores in healthy controls may be indicative of a ceiling effect which prevented us from finding any significant associations in the healthy control group.

There is a good reason to hypothesise that a lower cardiorespiratory fitness may contribute to a lower physical HRQL in people with BD. Since cardiorespiratory fitness might be limited centrally, by the capacity to delivery oxygen to the working muscles, and peripherally by the working muscles capacity to uptake and utilise oxygen, an impaired cardiorespiratory fitness is likely to impair the capacity to undertake daily activities without undue fatigue (Pate, 1988). When looking at the association of cardiorespiratory fitness with individual physical HRQL factors (data available upon request), we observed that those with lower levels of cardiorespiratory fitness also reported more physical limitations during activities of daily living, such as lifting or carrying groceries, climbing stairs, bending, kneeling, or stooping and walking one or several blocks. In contrast with the association with cardiorespiratory fitness, the level of physical activity participation was not significantly associated with physical HRQL. A possible explanation is that, although highly related, cardiorespiratory fitness and physical activity are two different constructs (Vanhees et al., 2005) resulting in different associations, a finding previously reported in people with schizophrenia (Vancampfort et al., 2015c) as well. An important distinction between physical activity and cardiorespiratory fitness lies in the relative variability of these two parameters. Whereas physical activity levels vary on a daily or weekly basis, cardiorespiratory fitness levels take longer to change (Vancampfort et al., 2015c). This variability impacts the ability to measure these two variables cross-sectionally, and consequently influences their relationship with physical HRQL.

Of interest, a lower cardiorespiratory fitness was also associated with a worse mental HRQL in outpatients with BD. A recent meta-analysis (Schuch et al., 2016) demonstrated that a better cardiorespiratory fitness was protective against developing depression. One potential mechanism to explain the protective role of cardiorespiratory fitness for a worse mental health may be related to the association between cardiorespiratory fitness and the functional connectivity of the brain (Douw et al., 2014). Functional connectivity is defined here as the temporal dependence of neuronal activity patterns of anatomically separated brain regions (Aertsen et al., 1989). For example, evidence suggests that cardiorespiratory fitness, regardless of physical activity levels, is associated with better functional connectivity between the different regions of the brain (Douw et al., 2014). It has been demonstrated recently (Lu et al., 2016; Brady et al., 2017) that bipolar mood states are associated with highly significant alterations in this functional connectivity and altered activities in neural networks may be biomarkers of BD diagnosis and mood state that are accessible to neuro-modulation and are promising novel targets for scientific investigation and possible clinical intervention. A better functional connectivity due to a better cardiorespiratory fitness may be potentially explained by mechanisms such as (a) the enhancement of the endothelial function and decrease arterial stiffness, oxidative stress and vascular inflammation (Davenport et al., 2012) and (b) the improvement of oxidative capacity, promoted by the improvement of the mitochondrial function and angiogenesis, allowing more exchange of neurotrophic factors, such as brain-derived neurotrophic factor (Voss et al., 2016).

#### *4.2. Strengths, limitations and future research*

Strengths of the current study are the use of gold-standard assessments for cardiorespiratory fitness and physical activity assessments. Nonetheless, the current findings should be considered in light of certain methodological limitations. The primary limitations of this pilot study are the limited sample size and the cross-sectional nature of the design, such that it was not possible to establish a direct cause and effect relationship. Future longitudinal studies are needed to extend the current findings. Second, all participants were on a stable medication dosage for at least 4 weeks, and we excluded acute psychotic patients or those with a substance use disorder in the previous 6-month period. It is unclear whether the current results would generalise to persons in more acute phases of illness or to those experiencing a first psychotic episode, or substance use disorder. Third, the different recall periods between the SF-36 and physical activity assessment used, should be considered as a limitation that

might affect any associations. While the SWA assessed physical activity and sedentary behaviour during the previous week, the SF-36 assesses the HRQL during the previous 4 weeks.

#### *4.3. Conclusions*

This study demonstrates that in people with BD cardiorespiratory fitness might be a contributor to the physical and mental HRQL. Associations between mental HRQL and cardiorespiratory fitness offer also novel targets for scientific investigation and possible lifestyle interventions in this vulnerable population.

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#### **Conflicts of interest**

None to report.

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**Table 1** Comparisons in characteristics between outpatients with bipolar disorder (n=20) and healthy controls (n=20)

Variables	bipolar disorder	healthy controls	P
Age (years)	47.9±7.9	47.8±7.6	0.95
BMI (kg/m <sup>2</sup> )	26.4±5.2	25.6±5.0	0.60
SF-36 HRQL physical component	71.2±18.7	94.5±3.8	<0.001*
SF-36 HRQL mental component	78.7±12.7	92.7±3.4	<0.001*
VO <sub>2</sub> max (ml/min/kg)	26.0±7.3	30.4±6.5	0.047*
SWA AEE (kcal/day)	650.9±314.5	731.2±306.0	0.42
SWA sedentary time (min/day)	1062.4±136.2	898.2±161.8	0.001*
PANAS positive affect (0-50)	30.5±9.1	36.9±6.8	0.015*
PANAS negative affect (0-50)	19.9±8.1	15.4±7.4	0.072

Data expressed as mean ± standard deviation, BMI = Body Mass Index, VO<sub>2</sub>max= maximum oxygen uptake, SWA AEE= SenseWear Armband Active Energy Expenditure, HRQL= Health Related Quality of Life; PANAS= Positive and Negative Affect Schedule, \*significant when P<0.05.

**Table 2** Correlations of the health related quality of life subcomponents with cardiorespiratory fitness, demographical and clinical variables in people with bipolar disorder (n=20) and healthy controls (n=20)

	bipolar disorder			healthy controls		
	Physical HRQL	P	Mental HRQL	P	Physical HRQL	P
VO <sub>2</sub> max (ml/min/kg)	0.55	<0.001*	0.57	<0.001*	-0.10	0.66
Age	-0.31	0.052	-0.26	0.10	-0.35	0.13
BMI	-0.33	0.042*	-0.24	0.13	-0.12	0.60
SWA AEE (kcal/day)	0.37	0.019*	0.37	0.020*	0.41	0.075
SWA sedentary time (min/day)	-0.46	0.003*	-0.48	0.002*	-0.36	0.12
PANAS positive affect	0.64	<0.001*	0.56	<0.001*	0.023	0.92
PANAS negative affect	-0.58	<0.001*	-0.50	0.001*	0.16	0.49
Chlorpromazine eq (mg/day)	-0.67	0.034*	-0.47	0.17	/	/

HRQL=Health Related Quality of Life, VO<sub>2</sub>max= maximum oxygen uptake, BMI = Body Mass Index, SWA AEE= SenseWear Armband Active Energy Expenditure, PANAS= Positive and Negative Affect Schedule, eq=equivalent (n=10), \*significant when P<0.05.

**Table 3** Backward regression analysis in people with bipolar disorder (n=20) with physical health related quality of life as the dependent variable

	<b>b</b>	<b>SE</b>	<b>Beta</b>	<b>t</b>	<b>P</b>
VO <sub>2</sub> max (ml/min/kg)	0.77	0.39	0.3	1.75	0.09*
PANAS negative affect score	-1.42	0.4	-0.61	-3.53	0.003*
Constant	79.57	17.62	/	4.52	<0.001*

All significant correlates in the univariate analyses were included in the model (i.e. maximum oxygen uptake, body mass index, active energy expenditure, sedentary time, PANAS scores, but we did not include Chlorpromazine equivalents as these were only available in a subgroup), b=unstandardised regression coefficient, beta=standardised regression coefficient, SE=standard error, VO<sub>2</sub>max=maximum oxygen uptake, PANAS= Positive and Negative Affect Schedule, \*significant when P<0.10.

**Table 4** Backward regression analysis in people with bipolar disorder (n=20) with mental health related quality of life as the dependent variable

	<b>b</b>	<b>SE</b>	<b>Beta</b>	<b>t</b>	<b>P</b>
VO <sub>2</sub> max (ml/min/kg)	0.63	0.34	0.36	1.84	0.08*
PANAS negative affect score	-0.76	0.31	-0.48	-2.43	0.03*
Constant	77.5	13.8	/	5.6	<0.001*

All significant correlates in the univariate analyses were included in the model (i.e. maximum oxygen uptake, body mass index, active energy expenditure, sedentary time, PANAS scores), b=unstandardised regression coefficient, beta=standardised regression coefficient, SE=standard error, VO<sub>2</sub>max= maximum oxygen uptake, PANAS= Positive and Negative Affect Schedule, \*significant when P<0.10.

#### Highlights

- Lower cardiorespiratory fitness may contribute to a lower mental and physical quality of life.
- Physical activity participation was not significantly associated with physical quality of life.